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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/305,084	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3 and 6-32* is/are pending in the application.

4a) Of the above claim(s) *6-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3 and 14-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/25/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4 and 5 have been canceled. Claims 1, 14-20 have been amended. Claims 21-32 have been added. Claims 1-3, 6-32 are pending. Claims 6-13, drawn to non-elected inventions are withdrawn from consideration. Claims 1-3 and 14-32 are under consideration.

2. The text of sections of Title 35, U.S. Code not found in the action can be found in a previous Office action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-3, 14-32. are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 1, 14-21 recite the limitation of "ETB selective antagonist". It is unclear how an ETB-selective antagonists differs from an ETB-specific antagonist of claims 22-32. It appears as though the limitation encompasses identical molecules in the case of claims 20 and 31.

(B) Claims 1, 15-18, 21, 22, 27-30 and 32 recite the limitation "small" molecule inhibitor. The term "small" in claims 1, 15-18, 21, 22, 27-30 and 32 is a relative term which renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(C) Claims 2 and 23 are drawn to an improper Markush group. Applicant is advise to reformat the claim reciting "ovarian cancer and mammary cancer" rather than "ovarian cancer or mammary cancer".

4. Claim 31 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 20. When two claims in an application are duplicates or else are so close in content that they both

cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). It appears that the terms "selective" versus "specific" do not change the scope of the claims because the same Markush group is recited in both claims

5. Claims 1, 2 and 14-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 2, 14-32 are rejected for the incorporation of new matter. Claims 1, 14-18, 20, have been amended to recite a compound that is a selective antagonist of the endothelin B receptor. Claim 14 has been amended to recite a cancer wherein said cancer expresses the endothelin B receptor and not the endothelin A receptor. Claims 15-18 has been amended to recite a compound that prevents the downregulation of E-cadherin, beta-catenin, p120CTN in the cancer cell, respectively. Claim 18 has been amended to recite the specific limitation of preventing the increased activity of caspase 8 in the cancer cell. Claim 21 has been amended to recite the preventing the downregulation of E-cadherin in the cancer cell.

New claims 22-32 contain the limitation of an ETB specific antagonist. rather than an ETB selective antagonist. Claims 22 and 25 comprises the specific limitation of an ETB specific antagonist. Claim 26 comprises the limitation of cancer cells which expresses the endothelin B receptor and not the endothelin A receptor. Claims 27-29 comprise the limitations of preventing the downregulation of E-cadherin, beta-catenin, and p120CTN, respectively. Claim 30 comprises the specific limitation of preventing the increased activity of caspase-8. Claim 32 comprises the limitation of preventing the downregulation of E-cadherin in a cancer cell.

With the exception of claim 3 and 24 all of the claims are broadly drawn to a method of inhibiting cancer. the specification states on page 15, lines 22-31 that the phenomenon of downregulation of E-cadherin, p120CTN and beta catenin proteins occurs in melanocytes and melamona cells through activation of the ETB receptor , and moreover that ET-1 transiently activates caspase-8 (page 15, lines 24-25). It is also noted that all the working examples to illustrate the above gene downregulations and activations deal with melanocytes and melanoma

cells. Accordingly, claims which are broadly drawn to the inhibition of cancer by means of interfering with these mechanisms constitute new matter. There is no support in the specification for the inhibition of all cancer cells by means of ETB specific or selective inhibitors, or methods of treating all types of cancers by administering an ETB antagonists which prevents the downregulation of E-cadherin, p120CTN and Beta-catenin. Further, the specification teaches only that melanomas loose the expression of ETA receptors (page 8, lines 20-21), thus the specific embodiments of claims 14 and 26, applied to any cancer cell, is new matter. Further, there is no antecedent basis for the limitation of ETB-selective antagonist in the specification or the claims as filed. One of skill in the art would reasonably conclude that applicant was not in possession of a method of broadly treating any cancer comprising the administration of an ETB-selective antagonist.. One of skill in the art would reasonably conclude that applicant was in possession of method of treating melanoma, but not a method of broadly treating any cancer comprising the administration of an ETB-specific antagonist.

6. Claims 1-3, 14-19, 21-30 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating cancers which express the ETB receptor to a greater extent than surrounding tissue, wherein said methods do not rely on anti-sense therapy, does not reasonably provide enablement for methods of treating cancer which do not express the ETB receptor to a greater extent than surround tissue, or methods of treating cancer which express the ETB receptor to a greater extend than surround tissues by means of antisense therapy . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

(A)As drawn to the treatment of cancers which express the ETB receptor to a lesser extent than surround non-cancerous tissues

The instant claims are broadly drawn to methods of treatment comprising the administration of ETB receptor antagonists (specific and selective, which has been rejected under 112, second above). The art recognizes that in metastatic cancers, such as metastatic melanoma (Kikuchi et al, Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739) or metastatic prostate cancer (Nelson et al, Cancer Research, 1996, vol. 56, pp.

663-668), the expression of the ETB receptor is reduced. The art teaches that as a cancer progresses, gene expression is altered so as to render said cells independent from paracrine growth signals (F. Meins, 'Cancer as a Problem in Development', In: Cancer: The Outlaw Cell, 1988, pp. 97-98). Kikuchi et al teach that down regulation of the ETB receptor in metastatic melanoma results in a loss of paracrine growth response to the natural ligands for the ETB receptor (page 739, lines 1-8) lending to metastasis to a distant site independent of ET ligands. Nelson et al point out that in metastatic prostate cancer showed decreased ETB binding relative to the surrounding tissues. One of skill in the art would reasonably conclude that administration of an ETB antagonist would not cause a therapeutic effect on metastatic cancer cells, or cancer cells that do not express the ETB receptor, because the antagonist would be taken up by normal cells to a greater extent that metastatic cells due to the low levels of the ETB receptor.

(B)As drawn to the treatment of cancers by anti-sense therapy

The claims are drawn in part to a method of inhibiting cancer comprising the administration of an ETB antisense molecule. The specification contemplates this application as gene therapy (section 5.3, pages 26-27). The specification does not reasonably provide enablement for the administration of an ETB antisense molecule or a ribozyme targeting the ETB receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and us the invention commensurate in scope with these claims.

In order to practice the full scope of the claims, the medical procedure of gene therapy must be enabled. However, the state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA

the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), . Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue

experimentation without reasonable expectation of success in order to practice the methods of claim 26 to the extent that it reads on gene therapy.

7. Claims 1, 2, 20, 22, 23 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Vournakis et al (US 6,063,911, priority to December 22, 1998, cited in a previous Office action).

Claim 1 is drawn in part to a method for treating cancer comprising administering to a patient in need thereof a compound which is a ETB selective antagonist, wherein said ETB selective antagonist is a peptide inhibitor and a small molecule inhibitor. Claim 2 embodies the method of claim 1 wherein the cancer is selected from the group consisting of melanoma, prostate, colon, ovarian or mammary cancer.

Claim 20 is drawn to a method for treating cancer comprising administering to a patient in need thereof an ETB selective antagonist selected from the group consisting of BQ788, IRL-1038 and RES-701-1.

Claim 22 is drawn in part to a method for treating a cancer comprising the administration of a ETB-specific antagonist wherein said ETB specific antagonist is selected from the group consisting of a peptide inhibitor and a small molecule inhibitor. Claim 23 embodies the method of claim 22 wherein the cancer is selected from the group consisting of melanoma, prostate, colon, ovarian and mammary cancer.

Claim 31 is drawn to a method of treating cancer comprising administering to a patient in need thereof an ETB specific antagonist selected from the group consisting of BQ788, IRL-1038 and RES-701-1.

Vournakis et al disclose a method for treating a cell proliferative disorder, including cancer, comprising administering to a patient a therapeutically effective amount of at least one endothelin antagonist in combination with a poly-beta-1-4-glucosamine (claims 28-30). Vournakis et al also disclose a method for treating cancer comprising administering to a patient a therapeutically effective amount of a non-peptide based endothlian antagonist in combination with a pharmaceutically acceptable carrier (claims 3-35). Vournakis et al disclose that targets for the disclosed pharmaceutical compositions include breast, GI tract, pancreatic, lung, urinary and uterine tumors (column 22, lines 46-62). Vournakis et al teach that peptide based endothelian antagonist of the disclosed methods include BQ-788, RES-701-1 and non-peptide endothelian

antagonists include RO 46-8443 (column 17, lines 15-35) which fulfill the specific embodiments of the claims.

It is noted that Vournakis et al teach against the specific embodiments of the instant claims drawn to melanoma. Vournakis et al states on column 30, lines 49-52 that the ETA agonist was able to significantly reverse the effects of 5 micromolar Ro61, which correlated well with the known higher affinity of Ro61 for ETA which would not lead one of skill in the art to conclude that selective inhibition of the ETB receptor would decrease proliferation melanoma cells.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-3 and 14-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739) in view of Nelson et al (Cancer Research, 1996, Vol. 56, pp. 663-668).

Kikuchi et al teach that contacting of BQ-788, a ETB antagonist with a primary melanoma cell line , PM-WK, which expresses high level of ETB receptors resulted in a significant decrease in the mitogenic activity stimulated by the ET-1 or ET-3 , but that contacting

with BQ-123 had no such effect (page 735, line 1 to page 746, line 2). Kikuchi et al teach that the ETB receptor subtype mainly initiates mitogenic signalling in primary melanoma (page 738, lines 6-8).

Nelson et al teach that Et-1 binding in vivo in inhibited by the ETB antagonist BQ-788, but not BQ-123 (a ETA antagonist).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer BQ-788 to a patient having a primary melanoma expressing the ETB receptor, or a recurrent melanoma expressing the ETB receptor. One of skill in the art would have been motivated to do so by the teachings of Kikuchi et al on the ability of BQ-788 to inhibit the growth of melanoma cells expressing the ETB receptor in the presence of ET-1 and ET-3 and the teachings of Nelson et al on the ability of BQ788 to bind to ETB receptors when administered in vivo. One of skill in the art would reasonably conclude that BQ788 would bind and antagonize the ETB receptor on primary or recurrent melanoma cells in vivo even in the presence of the endogenous ET-1 and ET-3 ligands.

10. All other rejections and objections as set forth in the previous office action are withdrawn in light of applicants amendments and arguments.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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03/08/04

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